REMARKS

Claims 1, 3-6, 8-11, 13-40, and 36-38, and 42-70 are pending in the above-identified patent application. Claims 22-35, 39 and 40 are withdrawn from consideration. Claims 1, 3-6, 8-11, 13-21, 42-46, 49-51, 54-61 and 64-70 stand rejected and claims 47, 48, 52, 53, 62 and 63 are objected to. In response, Applicant has amended Claims 1, 46, and 56, and cancelled Claims 20, 21, 66, and 67. Support for Claims 1 and 46 is found in the Specification, for example, at page 19, ll. 4-29, in Fig.1, in Table 2, and elsewhere.

Applicant's representatives thank the Examiner for the invaluable telephonic interview on May17, 2002 during which newly cited U.S. Patent No. 6,329,199 ("Pensiero") and suggestions for claim amendments were discussed.

Applicants invention is directed to production of human serum resistant retroviral particles (RVP). As set forth in the specification and in contrast to the prior art the Applicant shows that fully human serum-resistant RVPs can be made by choosing producer cells that are fully human serum-resistant.

Human serum resistant cells are set forth in the Specification, and are differentiated from partially resistant cells. For example, human serum resistant cells include Mpf, HT1080, MRC-5, HeLa, WISH and MDOK, which are set forth in Fig. 1 and Table 2 (see Specification, p. 30), whereas BHK cells are partially resistant. Accordingly, "fully human serum-resistant cells" should be taken to include cells that are more resistant than BHK cells. Similarly, human serum resistant cells that are resistant to 100% human serum are more resistant than BHK cells. Applicant believes that this interpretation is consistent with the scope of the invention while avoiding anticipation by cited prior art.

Objection under 37 C. F.R. 1.75(c)

Claims 58 and 63, have been objected to as improper for reciting a limitation (i.e. ". . . wherein the cell line exhibits no specific hybridization to a Moloney-MLV gag-pol or env probe") present in the claims from which they depend. In response, Claim 56 has been amended to correct a typographical error. Claims 58 and 63 appears to be proper, as the

limitation is not present in any of Claims 46 and 56, from which Claim 58 depends, or in Claims 46, 51, and 61, from which Claim 63 depends. Applicant respectfully requests that the objection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 3-6, 8-11, 13-21, 36-38, 42-45, 56-60 and 66 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification. The limitation reciting "... the non-primate mammalian cell line is not BHK." has been deleted from Claim 1. The rejection is therefore moot, and Applicant respectfully requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 20-21, 46, 49, 51, 54, 61 and 66-67 have been rejected as anticipated by Pensiero. Claims 20, 21, 66, and 67 have been cancelled without prejudice. With respect to the remaining claims, Applicant respectfully traverses the rejection. Pensiero does not disclose the presently claimed invention. The present invention is directed to production of human serum-resistant RVPs and cell lines useful for producing human serum-resistant RVPs. The specification shows that serum-resistant particles are produced by these serum-resistant cells. In particular, several cell lines are disclosed to be human serum-resistant when incubated in 100% human serum, as well as in diluted serum of 75, 50 and 25% (*see,* Example 2, page 19, ll. 11-26, Fig. 1 and Table 2). At best, only about 88% of Pensiero's Mv-1-Lu cells are serum resistant when incubated in 66% serum or 2/3 serum dilution (*see,* Pensiero et al., Figure 3). In addition, the Mv-1-Lu cells into which packaging vectors have been introduced, such as Mv-1-Lu/MLV-A, Mv-1-Lu/MLV-X and Mv-1-Lu/RD114, have equivalent (88% survival for Mv-1-Lu/MLV-X and Mv-1-Lu/RD114) or even lower survival (76% survival for Mv-1-Lu/MLV-A cells) in 66% serum (*see,* Pensiero et al., U.S. Patent No. 6,329,199, Figure 3). The survival of these cell lines in 66% serum is similar to survival of cell lines, e.g. Hak and BHK, disclosed in the present application that are partially resistant.

(*see*, Fig. 1). Thus, according to the present invention, Pensiero's MV-1-Lu cells are only partially resistant to diluted human serum and are not resistant to undiluted human serum.

Claims 46, 49-51, 54, 55, 61, and 64-70 have been rejected as anticipated by Rother et al. (U.S. Patent No. 5,871,997). The Examiner asserts that Rother uses the same methods of preparing stable retroviral packaging cell lines for the generation of RVPs.

This rejection is respectfully traversed. Rother teaches the use cell lines that do not express, or have been treated so as to prevent the synthesis of the galactose alpha (1,3) galactosyl (αGal) epitope. With respect to serum resistance, it appears that the disclosure provides no more than that the cells are "less prone to hyperacute rejection when exposed to body fluids," and are protected from damage mediated by antibodies in human or Old World primate body fluids that recognize a galactose alpha (1,3) galactosyl epoitope. (Col. 8, ln. 66-Col. 9, ln. 8). Resistance of PA317 producer cells to human serum depleted of anti-αGal antibodies is disclosed only for 20% (dilute) human serum (see Rother, Col. 11, ll. 20 - 30; Col 29, ll. 39 - 61; Fig. 5A). Human serum resistance is also disclosed for PA317 producer cells depleted for αGal (PA317 cells transduced with H-transferase; see Col. 31, ll. 17-42). For PA317/H-transferase cells, even though αGal expression was reduced more than 90%, a significant amount of serum sensitivity is apparent, even upon incubation in 20% human serum. (Col. 31, ll. 35-54; Fig. 7; Fig. 8)

According to the present invention, desired cells are human serum resistant in high concentrations of human serum. Applicant's data shows that the cells disclosed by Rother, whether αGal positive or αGal negative, are not human serum resistant, and that human serum-resistant cells can express and display αGal moieties (*see*, e.g., Specification, Fig. 1, Table 2). As disclosed and claimed, the present invention does not is not anticipated by Rother.

To summarize, neither Pensiero nor Rother discloses or claims human serum resistant cell lines for production of human serum-resistant RVPs according to the presently claimed invention. Applicant respectfully requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 68 and 69 are rejected under 35 U.S.C. § 103(a) as unpatentable over Pensiero in view of Rollins et al., 1997, Human Gene Therapy 7:619-626 (Rollins). Claim 70 is rejected as unpatentable over Pensiero in view of Rollins, further in view of Culver et al., 1992, Science 256:1550-1552. Applicants respectfully traverse the rejections and assert that they are moot in view of claims as amended. To establish a *prima facie* case of obviousness, all the claim limitations must be taught by the prior art. *See* M.P.E.P. § 2143.03. As argued above, the prior art does not disclose Applicant's claimed human serum-resistant cells. According, a *prima facie* case of obviousness is not made out, and Applicant requests that the rejections be withdrawn.

Conclusion

It is believed that the present application is in a condition for allowance which action is earnestly solicited. If the Examiner has any questions, he is invited to contact the undersigned.

Respectfully Submitted,

Dated: November 25, 2002

By: Lawrence P. Casson
Reg. No. 46,606

KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

Version of claims with markings to show changes made

1. (Thrice amended) A method for preparing a stable, retroviral packaging cell line for generation of human serum-resistant retroviral vector particles (RVP) which comprises

(a) introducing one or more packaging vectors into a fully human serum-resistant non-primate mammalian cell line, wherein said cell line exhibits no specific hybridization to a Moloney-MLV retrovirus *gag-pol* or *env* probe and is capable of producing human-serum-resistant RVP and wherein said vectors, either singly or collectively, express a cellular targeting protein and retroviral *gag* and *pol* genes in amounts sufficient to package said RVP; and

(b) recovering said packaging cell line[;

with the proviso that the non-primate mammalian cell line is not BHK].

46. (Twice amended) A method for preparing a stable, retroviral packaging cell line for generation of human serum-resistant retroviral particles (RVP) which comprises

(a) introducing one or more packaging vectors into a [human serum-resistant] non-primate mammalian cell [line] that is human serum resistant in 100% human serum, wherein said vectors, either singly or collectively, express a cellular targeting protein and retroviral *gag* and *pol* genes in amounts sufficient to package said RVP; and

(b) recovering said packaging cell line.

56. (Amended) A method for preparing human serum-resistant retroviral vector particles (RVP) which comprises:

(a) introducing a retrovirus vector into the packaging cell line of Claim [1] 46, wherein said retrovirus vector is capable of being packaged into an RVP and comprises a heterologous gene capable of expression in a human;

(b) culturing said cell line for a time and under conditions sufficient to produce said RVP; and

(c) recovering said RVP.